REMARKS/ARGUMENTS

Prior to entry of this amendment, claims 1-3, 5-8, 21-25, 27-39, 41 and 43-46 were pending and rejected. Claim 30 is amended. Support is found throughout the specification and in the claims as filed. Claims 21-25, 27-29, 34, and 46 have been canceled without prejudice. Applicants specifically reserve the right to pursue one or more canceled claims in subsequently filed divisional or continuation applications.

Interview Summary

Applicants appreciate the Examiner's telephonic interview on November 2, 2005. In the interview the teachings of the Shi reference were extensively discussed in view of the pending claims. Agreement was not necessarily reached. However, Applicants note that the interview did elucidate some of the Examiner's issues with respect to Shi, which will be addressed in more detail below.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 2, 5, 6, 21, 22, 27-34 and 46 stand rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al. (PCR Meth. Appl., vol. 3, pp. 46-53, 1993). Applicants respectfully traverse the rejection.

As has been noted before, anticipation requires that each and every element of a claim is described in a single prior art reference, either expressly or inherently. *See* MPEP 2131 *citing Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Furthermore, the elements must be arranged as required by the claim. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

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Shi discloses a PCR based method for constructing a gene. Specifically, Shi teaches a method for constructing Lym-1 antibody variable regions. The method of Shi includes providing several PCR primers that overlap with either an upstream target sequence, a downstream target sequence, or with each other, amplifying to extend overlapping templates and primers and then performing a final PCR step to amplify the full length sequence.

In contrast, claim 1 requires a method that includes performing a first amplification step to amplify a first target fragment of DNA with a first primer pair, wherein the first primer pair, upon such amplification, adds to first and second ends of *the first fragment* predetermined first and second regions of complementarity to form a second DNA fragment having said first region of complementarity at a first end and a second region of complementarity at a second end of said second DNA fragment. The claim further requires, *inter alia*, providing a promoter-containing sequence and a terminator-containing sequence, said promoter-containing sequence further including a region complementary to said first region of complementarity and said terminator-containing sequence including a region complementary to said second region of complementarity. Thus, the claim requires adding to first and second ends of a DNA fragment, first and second regions of complementarity that are subsequently hybridized with primers containing a promoter containing sequence and terminator containing sequence, respectively.

However, Shi fails to teach such a method.

First , Applicants note that Shi fails to teach the addition of a promoter containing region and a terminator containing region to a target nucleic acid. Specifically, Table 2 of Shi discloses the various primers used. As discussed recently in the interview with the Examiner on November 2, 2005, it was agreed that primer 10, "BSH" primer, includes the termination sequence. As shown in Figure 1, primer 10 is only used as a primer in the last step of the amplification. Primer 10 is used in conjunction with primer 2, "EOP" primer, to amplify the fused sequence. However, Applicants submit that primer 2 does not include a promoter sequence. Rather, the promoter containing primer(s) are Primers 1 (possibly) and Primers 3 and 4. This is outlined on the enclosed marked up version of Shi's Figure 6 that highlights the sequences of the different primers in the fused gene and denotes the location of the various

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functional regions, e.g. the promoter and terminator containing regions. As discussed, Applicants submit that this identifies notable differences in the Applicants' claim that requires adding to first and second ends of a DNA fragment, first and second regions of complementarity that are subsequently hybridized with primers containing a promoter containing sequence and terminator containing sequence, respectively, that sets forth methods distinct and distinguishable from the method of Shi.

As can be seen in Figure 1, the promoter containing primer(s) are fused to the target "Amplified V_L" sequence in a "PCR first step". The terminator containing primer is not fused with this "Amplified V_L" sequence. Rather, as noted above, it is used to amplify the fused product.

Thus, to reiterate, while claim 1 and those that depend from claim 1 require the addition of promoter and terminator to "a target" to which regions of complementarity were added, such a method is not taught in Shi for a variety of reasons. The promoter containing primer(s) and terminator containing primer are added to distinct target nucleic acids, e.g. not the same target nucleic acid as required by the claims. For at least this reason, Shi fails to anticipate these claims.

Regarding the rejection of claim 21, 22, 27-29, 34 and 46, Applicants submit that the rejections are moot as the claims have been canceled.

With respect to the rejection of claims 30-33 Applicants traverse the rejection.

Claim 30 is directed to a system for adding a nucleic acid fragment that confers function to a polynucleotide target sequence. The system includes an extension primer pair that adds a 5' region of complementarity and a 3' region of complementarity to the target. In addition, the system includes a 5' biological function conferring nucleic acid fragment that includes a promoter and a 3' region of complementarity that includes a terminator.

However, as noted above, Applicants submit that Shi fails to disclose system. For the reasons set forth previously, namely that Shi fails to disclose primer pair wherein the primers are complementary to regions of complementarity added to a target nucleic acid, Applicants submit

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that Shi fails to teach each element of the claims. In fact, the promoter containing primer(s) and terminator containing primer of Shi are added to different nucleic acid molecules. Thus, the system as disclosed in Shi fails to anticipate the rejected claims.

For the above reasons, Applicants submit that Shi fails to anticipate any of the pending claims. Applicants respectfully request the Examiner to withdraw the rejection.

Rejection Under 35 U.S.C. § 103

Claims 3, 23, and 35 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (described above) and Felgner, et al., (U.S. Patent No. 6,165,720). Applicants respectfully traverse the rejection.

Shi, et al. is described above. Felgner, et al. discloses construction of nucleic acid vectors containing a PNA-binding site. Thus, according to the Examiner, the combination of the references renders claims 3, 23, and 35 unpatentable.

The Applicants respectfully submit that the Examiner has failed to make out a *prima facie* case of obviousness. In order to establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, there must be some suggestion or motivation, either in the cited references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); M.P.E.P. § 2142; *Cf. Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 U.S.P.Q.2d 1161 (Fed. Cir. 1999). Second, the proposed modification of the prior art must have a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q. 1016, 1023 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991); *In re Erlich*, 22 U.S.P.Q. 1463, 1466 (Bd. Pat. App. & Int. 1992); *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970); M.P.E.P. § 2142.

Here, Applicants submit that the combination of references fails to disclose each element

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of the claims. Specifically, as noted above in the response to the 102 rejection, Shi fails to disclose that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to *a target sequence*. The method in Shi fails to teach such a method because the promoter containing primer (s) and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA.

Moreover, Felgner does not provide any disclosure that would cure the defect of Shi et al. That is, as noted by the Examiner, Felgner discloses construction of nucleic acid vectors (or plasmids) containing PNA-binding sites. However, such a disclosure fails to cure the deficiencies of Shi et al. Accordingly, Applicants submit that the claims are not rendered obvious in light of the references taken individually or when combined because the combination of references fails to teach each element of the rejected claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 7, 8, 24, 25, 36 and 37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Uhlman, et al. (U.S. Patent No. 6,063,571). Shi, et al. is described above. According to the Examiner, Uhlman et al. disclose amplification of nucleic acids with DNA/PNA primers. Thus, according to the Examiner, the combination of the references renders claims 7, 8, 24, 25, 36 and 37 unpatentable. Applicants respectfully traverse the rejection.

As noted above, Applicants submit that Shi fails to teach that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because promoter containing primer(s) of Shi and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA.

Moreover, Uhlman does not provide any disclosure that would cure the defect of Shi et al. As the Examiner noted, Uhlman discloses amplification of nucleic acids with DNA/PNA

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primers, but this disclosure fails to cure the deficiencies of Shi et al. Accordingly, Applicant submit that the claims are not rendered obvious in light of the references taken individually or when combined because the combination of references fails to teach each element of the rejected claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 38, 39, 41 and 43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Mullis, et al. (U.S. Patent No. 4965188). Applicants respectfully traverse the rejection.

Shi, et al. is described above. According to the Examiner, Mullis discloses polymerase chain reaction (PCR) such that more than one target nucleic acid can be amplified using primers specific for its target.

However, as noted previously, Shi fails to disclose that the promoter containing sequence and terminator sequence hybridize to first and second regions of complementarity, respectively, that were added to a target sequence. The method in Shi fails to teach such a method because promoter containing primer(s) of Shi and the terminator containing primer do not contain regions of complementarity that would hybridize to regions of complementarity that were added to the *same* initial target DNA. Moreover, Applicants submit that while Mullis discloses a PCR method, there is no disclosure in Mullis that cures the deficiency of Shi et al.

In addition, Applicants note that the claim 38 recites the step of "creating extension primer pairs for each of a plurality of different target polypeptide-encoding sequences, each extension primer pair comprising first and second extension primers, respectively comprising first and second extension regions and a region of complementarity to a particular target sequence, such that the first and second extension regions for each extension primer pair are the same as the first and second extension regions for the other of said extension primer pairs, but the regions of complementarity are customized for each target sequence".

However, Applicants submit that neither Shi, nor Mullis, nor the combination of the references teaches such a step. That is, Shi fails to disclose amplification of multiple target nucleic acids with primers that contain the same 5' extension regions and regions of

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complementarity that are customized to a particular target sequence. In addition, Mullis fails to teach such a method. While it is true that Mullis discloses that the primers may have sequences non-complementary to the target attached at the 5' ends of the primers, this in no way teaches or suggests that the 5' ends of the primers contain the same 5' extension regions among all of the primers.

For all of the above reasons, Applicants submit that the references individually or in combination fail to teach each element of the claims. Applicants respectfully request the Examiner to withdraw the rejection.

Claims 44 and 45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Shi, et al. (cited above) and Uhlman, et al. (U.S. Patent No. 6,063,571).

Claim 44, as amended, recites, *inter alia*, that each of the third and fourth nucleic acid fragments comprises a nucleic acid region that confers function. Also, following a second PCR amplification reaction, the first and second functional nucleic acid regions are joined to the polynucleotide target sequence.

However, as noted previously, Shi fail to disclose such a method wherein first and second functional sequences are attached to the same target nucleic acid. Moreover, as noted previously, while Uhlman discloses amplification with DNA/PNA primers this in no way cures the deficiency of Shi et al, as described above.

Accordingly, Applicants submit that the rejection in light of Shi and Uhlman has been overcome. Applicants respectfully request the Examiner to withdraw the rejection.

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CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (referencing Attorney's Docket No. **40019-0008**).

Respectfully submitted,

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EXHIBIT A

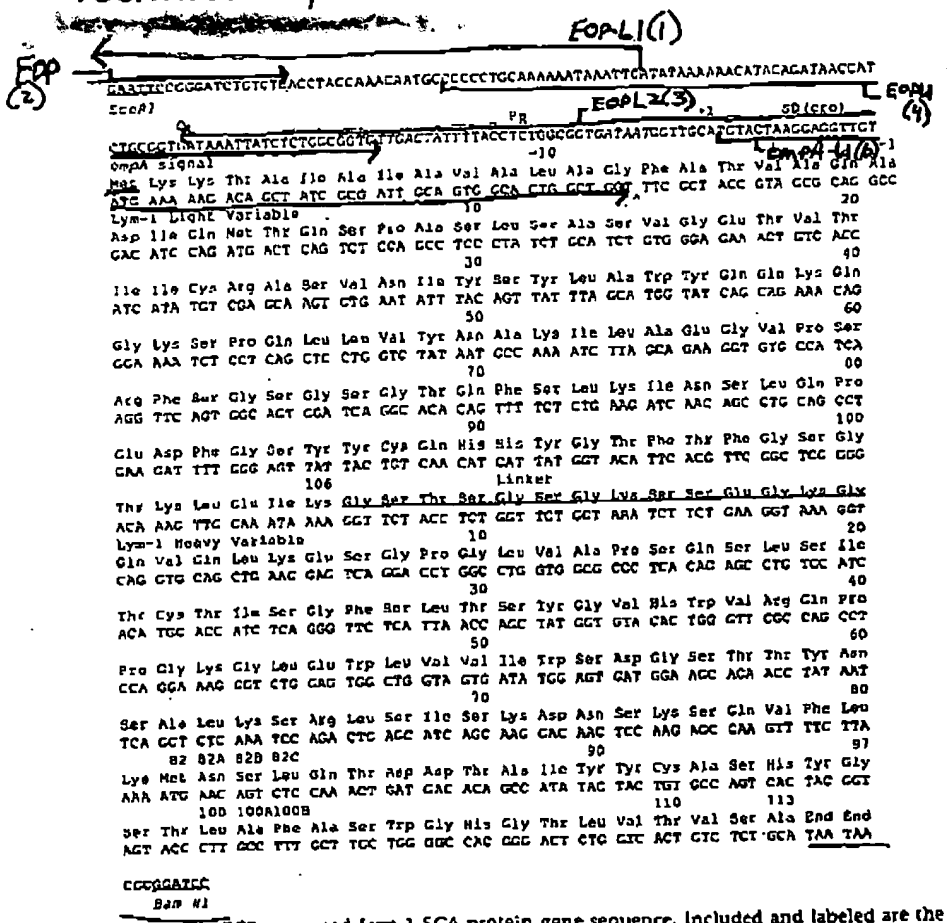

FIGURE 6 The PCR-generated Lym-1 SCA protein gene sequence. Included and labeled are the o_L/p_R promoter, *ompA* signal sequence, Lym-1 V_L and V_H, and a 14-amino-acid linker (underlined).

quenced using Sequenase 2.0 according to the supplier's protocol. The sequence of the gene is shown in Figure 6.

DISCUSSION

Here, we describe a strategy for amplifying the V_H and V_L genes of Lym-1. The variable regions of antibody genes convey antibody specificity; thus, it is critical to accurately reproduce the variable regions of both the heavy and light chains in preparation for engineered antibodies. In agreement with other researchers,[12,27] we have demonstrated the success of using consensus primers in the amplification of antibody variable region genes. The genes were sequenced by three independent protocols and no discrepancies were detected.

The PCR technique has been used to construct and/or amplify genes by several approaches.[13–18,28] In this paper we extend the strategy to construct a 954-bp Lym-1 SCA protein gene using nine synthetic oligonucleotides and two PCR-produced V_H and V_L coding regions by a two-step PCR method. We demonstrate that the strategy greatly simplifies the time-consuming process of preparing a recombinant gene.

Taq DNA polymerase lacks 3′-exonucleolytic proofreading activity. In agreement with other researchers,[29,30] we found that the fused products produced by the *Taq* enzyme contained errors, including base substitutions, deletions, and insertions (data not shown). The fused gene prepared by *Vent*$_R$ DNA polymerase, which has the 3′ → 5′ exonuclease proofreading activity, was introduced into the vector by restriction cloning, and the correct nucleotide sequence was produced.

The advantages of this strategy include its simplicity, speed, efficiency, and low cost. Construction of a gene by PCR fusion eliminates the need for incorporation of internal restriction sites to assemble the gene. Except for insertion into the cloning vector, neither restriction enzymes nor ligase are needed. The two-step PCR recombination can be performed in a single day. DNA can be prepared in microgram quantities. No purification is required, and the product can be directly introduced into the TA cloning vector. Although we constructed a PCR fusion gene of 954 bp, it seems that longer DNA fragments can be generated by the same strategy. In addition, the technique can be applied to genes other than antibodies.

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